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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/398,610	09/17/1999	MICHAEL D. EDGE	10275/137001	1306

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EXAMINER	
BECKERLEG, ANNE M	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/398,610	EDGE ET AL.	
	Examiner	Art Unit	
	Anne M Beckerleg	1632	

-- The MAILING DATE of this communication appears on th cov r sh t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 16-35* is/are pending in the application.

4a) Of the above claim(s) *9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-14 and 16-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment and response received on 3/25/02 has been entered. Claim 15 has been canceled. New claims 18-35 have been entered. Claims 1-14, and 16-35 are pending in the instant application. This application contains claim 9 which is drawn to an invention non-elected without traverse in paper no. 8. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Claims 1-8, 10-14, and 16-35 are under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this office action, can be found in previous office actions.

Claim Objections

The objections to claims 5 and 17 have been overcome by applicant's amendments to the claims.

Claim Rejections - 35 USC § 101

The rejection of claims 16 and 17 under 35 U.S.C. 101 is withdrawn in view of applicant's amendments to the claims.

Claim Rejections - 35 USC § 112

The rejections of claims 14-16 under 35 U.S.C. 112, second paragraph, have been withdrawn in view of applicant's cancellation of or amendment to the claims.

Claim Rejections - 35 USC § 103

The rejection of original claims 1-8 and 10-17 under 35 U.S.C. 103(a) over U.S. Patent No. 5,959,171, hereafter referred to as Hyttinen et al., in view of Zewe et al. is withdrawn in view of applicant's amendments to the claims. Please note however that claims 1-8, 10-14, and 16-35 are subject to rejection under 35 U.S.C. 103 below.

Applicant's amendments have necessitated the following new grounds of rejection.

Claims 1-8, 10-14, and 16-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,959,171, 9/28/99, filed on 8/17/94, hereafter referred to as Hyttinen et al., in view of Rybak et al. (1992) PNAS, Vol. 89, 3165-3169. The applicant claims a vector encoding a mammary epithelial specific promoter, a signal sequence that directs the secretion of a fusion protein, and a fusion protein that comprises angiogenin, a transgenic animal which

comprises said vector, and methods of making a fusion protein providing a transgenic animal which expresses a fusion protein comprising angiogenin, and recovering the fusion protein from the milk of the transgenic animal. The applicant also claims said methods wherein the fusion protein comprising angiogenin further comprises a subunit of an Ig specific for a tumor antigen selected from a group which includes transferrin receptor. The applicant further claims said transgenic animals and methods wherein the fusion protein is secreted into the milk of the transgenic animal at concentrations of at least about 1 mg/ml.

Hyttinen et al. teaches vectors encoding a fusion protein operatively linked to regulatory elements needed for high level mammary gland specific expression derived from a milk protein gene or a mammary tumor virus and a DNA sequence encoding a signal sequence needed for secretion and maturation of the fusion protein (Hyttinen et al., column 3). Hyttinen et al. also teaches transgenic animals, including cows and goats, made using said vectors, and methods of making a bioactive fusion protein comprising collecting milk from a transgenic mammal which expresses a fusion protein in its milk, and isolating the recombinant fusion protein from the milk (Hyttinen et al., columns 3 and 5). Hyttinen et al. further teaches that making and using a transgenic mammal which expresses a beta-lactoglobulin-hEPO fusion protein at concentrations of 0.2-1 mg/ml in the transgenic milk (Hyttinen et al., column 10, lines 30-35). hEPO is an enzyme.

Hyttinen also teaches that the general idea of making and using transgenic bioreactors for the production of large quantities of proteins, particularly human proteins, was suggested as early

as 1986 and that numerous examples of transgenic bioreactors exist in the art, citing references from 1991-1992 (Hyttinen et al., column 1). Thus, Hyttinen establishes that the art recognized the advantages of producing large quantities of biologically relevant, therapeutic proteins in milk of transgenic animals.

Although Hyttinen et al. teaches general methods for making transgenic animals comprising enzyme fusion proteins and methods of making and isolating fusion proteins from the milk of transgenic mammals, Hyttinen et al. differs from the instant invention by not specifically teaching the production of a fusion protein comprising angiogenin. Rybak et al. supplements Hyttinen et al. by teaching nucleic acid expression constructs which encode a secretable fusion protein comprising a single chain antibody against the human transferrin receptor and angiogenin (Rybak et al., abstract). Rybak et al. also teaches that the isolated fusion proteins are capable of inhibiting protein synthesis in human tumor cell lines (Rybak et al., page 3165). While Rybak et al. teaches the expression of the fusion protein in mammalian cell lines in vitro, the skilled artisan would have been motivated to express the fusion protein taught by Rybak et al. using a mammalian bioreactor system in order to produce larger quantities of the human fusion protein as taught by Hyttinen et al. Therefore, in view of the benefits of using a transgenic bioreactor to produce large quantities of a protein for use in humans, it would have been prima facie obvious to the skilled artisan to express the fusion protein taught by Rybak et al. using the transgenic bioreactors taught by Hyttinen. Further, based on successful use of transgenic bioreactors in expressing large quantities of a variety of human proteins and enzyme containing fusion proteins

as taught by Hyttinen et al., the skilled artisan would have had a reasonable expectation of success in expressing the fusion protein comprising the a single chain antibody against the transferrin receptor and angiogenin in the milk of a transgenic mammal according to the methods taught by Hyttinen et al.

Applicant's arguments concerning the teachings of Hyttinen et al. in regards to the withdrawn rejection of the claims over Hyttinen in view of Zewe have been considered and addressed as they relate to the new grounds of rejection. The applicant argues that Hyttinen teaches a fusion protein comprising an inactive enzyme and therefore teaches away from the instant invention which recites an active enzyme. Hyttinen et al. however, clearly teaches that the fusion protein comprising the enzyme can contain an inactive enzyme or a biologically less active enzyme (Hyttinen et al., column 2, lines 32-54). Hyttinen therefore clearly teaches fusion protein which comprise an active enzyme.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé